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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/613,038	07/10/2000	Antonio J. Grillo-Lopez	P1752R1	9334

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EXAMINER
NGUYEN, QUANG

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 03/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/613,038	GRILLO-LOPEZ ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6/13/02; 8/13/02 and 12/30/02* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-16,22 and 28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-16,22 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12-14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet* .

Continuation of Attachment(s) 6). Other: IDS Paper Nos. 18-19, 22 and 24.

DETAILED ACTION

Applicants' amendment filed on June 13, 2002 in Paper No. 16, and the supplemental amendments filed on August 13, 2002 in Paper No. 20 and on December 30, 2002 in Paper No. 23 have been entered.

Amended claims 1, 5-16, 22 and 28 are pending in the present application.

Accordingly, claims 1, 5-16, 22 and 28 are pending in the present application.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior Office Action.

Inventorship

In view of the papers filed on June 13, 2002, the inventorship in this nonprovisional application has been changed by the deletion of Timothy A. Stewart.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of the file jacket and PTO PALM data to reflect the inventorship as corrected.

Information Disclosure Statement

Most of the references cited in the IDS filed on Nov 20, 2000 in Paper No. 5 have not been considered because they are not present in the application. The missing references have been filed on June 11, 2002 in Paper No. 14. However, these missing references are still not with the application. Applicant is requested to hand-deliver to the Examiner the missing references for their consideration.

Following is a new ground of rejection necessitated by Applicants' amendment.

Claim Rejections - 35 USC § 112

Amended claims 1, 5-16, 22 and 28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

Amended claims 1, 5-16 and 22 are drawn to a method of blocking an immune response to a graft in a mammal, wherein the mammal is not suffering from a malignancy, comprising administering to the mammal a therapeutically effective amount of an antibody which binds to CD20; the same method with various limitations recited in the dependent claims.

Amended claim 28 is directed to a method of treating graft-versus-host or host-versus-graft disease in a mammal comprising administering to the mammal a therapeutically effective amount of an antibody which binds to CD20.

The instant specification teaches by exemplification a prophetic example (example 3) in which an anti-CD20 antibody such as RITUXAN may contribute to the prevention of an allorejection response by inhibiting alloantibody production and/or affecting alloantigen presentation through depletion of antigen-presenting cells. Applicants further teach that the anti-CD20 antibody may also be combined with other induction immunosuppressive drugs such as polyclonal anti-lymphocyte antibodies or monoclonal anti-CD3 antibodies; maintenance of immunosuppressive drugs, such as calcinuerin inhibitors, anti-proliferative agents or combination regimens that include blockade of T cell co-stimulation, blockade of T cell adhesion molecules and blockade of T cell accessory molecules.

The above evidence has been noted and considered. However, the instant specification is not enabled for the presently claimed invention for the reasons discussed below.

When read in light of the specification, the instant claims encompass the **reduction or prevention** (the scope of blocking, see page 4, lines 27-28) of at least one immune-mediated response to a graft in a mammal not suffering from malignancy and for **treating** (encompassing **both therapeutic and prophylactic effects**, see page 16, lines 10-11) graft-versus-host or host-versus-graft disease in a mammal using an effective amount of an antibody which binds to CD20.

(1) The state of the prior art. At the effective filing date of the present application, apart from the utilization of rituximab, a chimeric murine-human monoclonal antibody directed against CD20, for the treatment of B-cell lymphoma, the use of rituximab or any other anti-CD20 antibody in other *in vivo* applications (e.g., graft transplantation or for treating graft-versus-host or host-versus-graft disease) was still very limited and further investigation is required (Leget et al., Curr. Opin. Oncol. 10:548-551, 1998; IDS; Friend et al., Transplantation 68:1625-1631, 1999; Cited previously). With respect to the use of bio-engineered monoclonals in transplantations, Friend et al. state "Monoclonal antibodies have proved to be of immense importance from a diagnostic and investigative standpoint. However in clinical transplantation their impact on therapeutic regimens have been rather disappointing" (page 1625, col.1, first paragraph).

(2) The amount of direction or guidance provided and the unpredictability of the art. In light of the state of the prior art at the effective filing date of the present application, there is no evidence of record indicating or suggesting that the use of rituximab or any other anti-CD20 antibody would be effective in reducing or preventing the host humoral and/or T cell-mediated immune responses against a graft (the graft must be allogeneic or xenogenic) or for treating any graft-versus-host or host-versus-graft disease in a mammal to an extent that the graft would be survived and maintained for a sufficient period of time to yield any beneficial use. The instant specification offers no guidance for a skilled artisan on how to target rituximab specifically to a B cell population that produces alloantigen or xenoantigen antibodies against a graft or to a

graft antigen presenting cell population or a donor T cell population in a graft such that these cell populations would be depleted or eliminated so that the desired therapeutic effects contemplated by Applicants could be achieved. Even in the B-cell lymphoma treatment studies with rituximab, despite the depletion of normal B cells, treated patients are still capable of eliciting an immune response against the humanized rituximab, even though it is at a low level (Leget et al., see abstract). Moreover, it is noted that rituximab has no effect on the total mean serum IgG and IgA levels of patients treated with the humanized monoclonal antibody (Leget et al., page 550, col. 1, first paragraph; Levine et al., Neurology 52:1701-1704, 1999; IDS, see page 1704). Furthermore, Wilkes et al. (Transplantation Proceedings 29:1891-1895, 1997) disclose that the production of IgG2 antibodies plays an important role in human lung allograft rejection. Therefore, it is unclear how the persistence of unaffected serum IgG and IgA levels in patients already treated with rituximab, and the ability of the treated patients to elicit an immune response against rituximab would not result in any adverse host immune response to a graft, so that the therapeutic and prophylactic effects contemplated by Applicants could be attained in the methods as claimed. It should be noted that the physiological art is recognized as unpredictable (MPEP 2164.03).

(3) The absence of a working example. Apart from a prophetic example 3 in which an anti-CD20 antibody such as RITUXAN may contribute to the prevention of an allorejection response by inhibiting alloantibody production and/or affecting alloantigen presentation through depletion of antigen-presenting cells, it is unclear whether the prevention or alleviation of any graft rejection via the utilization of any anti-CD20

antibody could be actually attained, particularly in light of the state of the prior arts discussed above.

(4) The breadth of the claims. The instant claims also encompass any route of administering an antibody that binds to CD20 into a mammal not suffering from a malignancy or a mammal having a graft-versus-host or host-versus-graft disease to obtain the desired therapeutic effects. The instant specification is not enabled for such a broadly claimed invention because it offers no guidance on how to achieve the desired results via intravenous delivery of rituximab as discussed above, let alone any route of delivery for an antibody that binds to CD20 (e.g., oral, subcutaneous or mucosal deliveries). The prior art at the effective filing date of the present application does not provide such guidance, therefore it is incumbent upon the instant specification to do so. With the lack of guidance provided by the present disclosure, it would have required undue experimentation for one skilled in the art to make and use the claimed invention.

Additionally, the breadth of the instant claims encompasses the utilization of any antibody that binds to CD20 to attain the desired therapeutic effects contemplated by Applicants for the methods as claimed. However, apart from the disclosure of anti-CD20 monoclonal antibodies known in the art, the instant specification fails to provide sufficient guidance for a skilled artisan on how to make and use any anti-CD20 polyclonal antibody possessing the same biological activities as those of the well-characterized chimeric monoclonal antibody rituximab in order to attain the therapeutic effects contemplated by Applicants for the claimed methods. Given the lack of sufficient

guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make and use the methods as claimed. Even among the disclosed monoclonal antibodies, apart from the well-characterized chimeric rituximab monoclonal antibody, Anderson et al. (U.S. Patent No. 5,736,137; Cited previously) note that non-human monoclonal antibodies (mouse monoclonal antibody 1F5) typically lack human effector functionality, e.g., they are unable to mediate complement dependent lysis or lyse human target cells through antibody dependent cellular toxicity or Fc-receptor mediated phagocytosis, and that non-human monoclonal antibodies can be recognized by the human host as a foreign protein and they are in effect neutralized before they reach their target site (see line 46 of col. 3 continues to line 3 of col. 4). It is also known that patients with B cell malignancies are immunosuppressive due to the nature of the disease. Therefore, in a mammal not suffering from a malignancy or in a mammal suffering from a graft-versus-host or host-versus-graft disease, would any anti-CD20 mouse monoclonal antibody, including the chimeric anti-CD20 monoclonal antibody rutuximab, not be neutralized or destroyed by a treated mammal prior to any contemplated therapeutic effects contemplated by Applicants could be achieved? And how any mouse monoclonal antibody that lacks human effector functionality as noted by Anderson et al. would alleviate or prevent an immune response to a graft or treating a graft-versus-host or host-vesus-graft disease in a human as encompassed by the instant claims?

As set forth in In re Fisher, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the unpredictability of the physiological art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant claimed invention.

Responses to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on filed on June 13/2002 in Paper No. 16 (pages 5-6) have been fully considered.

Applicants simply assert that the presently claimed invention is enabled by referring to various passages describing the instant invention and to example 3. With respect to the cited references of Friend et al. and Leget et al., Applicants argue that the Friend reference is concerned with an anti-CD3 antibody and not to anti-CD20 antibody, while the Leget reference is not relevant to the present invention because the claims specifically exclude the mammal which is suffering from a malignancy. Applicants' arguments are respectfully found to be unpersuasive for the following reasons.

Firstly, the mere description on how Applicants want to attain the desired therapeutic effects for the methods as claimed and a prophetic example 3 are not reasonably correlated to the therapeutic effects actually attained for the claimed methods for the various reasons already discussed above.

Secondly, with respect to the Leget reference, even in patients suffering B-cell lymphoma being treated with rituximab, despite the depletion of normal B cells, treated patients are still capable of eliciting an immune response against the humanized rituximab, and that rituximab has no effect on the total mean serum IgG and IgA levels, and knowing that patients with B cell malignancies are immunosuppressive due to the nature of the disease, then it would be very likely that an anti-CD20 antibody, including rituximab would be neutralized or destroyed in a mammal not suffering from a malignancy, so that the desired therapeutic and prophylactic effects contemplated by Applicants could not be attained in the methods as claimed. Moreover, since the total mean serum IgG and IgA levels are unaffected by the rituximab treatment, these antibody levels would be expected to have deleterious effects on a graft in a mammal, particularly the production of IgG2 antibodies plays an important role in human lung allograft rejection as evidenced by the teachings of Wilkes et al. Therefore, the Leget reference is relevant to the nature of the presently claimed invention.

Thirdly, with respect to the Friend reference, it reflects the state of the prior art on the use of bio-engineered monoclonals in transplantations at the effective filing date of the present application, with the use of a humanized CD3 antibody in renal transplant as a specific example. Therefore it is relevant to the presently claimed invention which encompasses the utilization of a chimeric mouse-human anti-CD20 monoclonal antibody among others to block an immune response to a graft in a mammal and for treating a graft-versus-host or host-versus-graft disease in a mammal. As Friend et al. state "Monoclonal antibodies have proved to be of immense importance from a

diagnostic and investigative standpoint. However in clinical transplantation their impact on therapeutic regimens have been rather disappointing" (page 1625, col.1, first paragraph), coupled with the lack of sufficient guidance provided by the instant specification for the various issues discussed above, it would have required undue experimentation for a skilled artisan to make and use the methods as claimed.

Accordingly, amended claims 1, 5-16, 22 and 28 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Amended claim 13 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the same reasons already set forth in the previous Office Action.

The term "a dose substantially less than 375mg/m^{2}" in claim 13 is a relative term which renders the claim indefinite. The term "a dose substantially less than 375mg/m^{2}" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Would a dose of 275 mg/m^{2}, 300 mg/m^{2} or 325 mg/m^{2} be considered to be substantially less than 375mg/m^{2}? The metes and bounds of the claim are not clearly determined.

Responses to Arguments

Applicants' argument related to the above rejection in the Amendment filed on filed on June 13/2002 in Paper No. 16 (page 7) has been fully considered.

With respect to claim 13, Applicants argue that the skilled clinician would readily understand what was intended by the expression "a dose substantially less than 375mg/m^{2}" in terms of a therapeutic dose. Applicants' argument is respectfully found to be unpersuasive because the lower limit of a dose substantially less than 375mg/m^2 is not clearly defined, therefore the metes and bounds of the claim are not clearly determined. For example, would a dose of 275 mg/m^2, 300 mg/m^2 or 325 mg/m^2 be considered to be substantially less than 375mg/m^2? Or only a dose less than 200 mg/m^2 or 100 mg/m^2 would be considered to be substantially less than 375mg/m^2.

Conclusions

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (703) 308-1906, or SPE, Remy Yucel, Ph.D., at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to LIE, Tiffiany Tabb, whose telephone number is (703) 605-1238.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER